Pain Complaints in Patients with Fibromyalgia Versus Chronic Fatigue Syndrome

Laurence A. Bradley, PhD, Nancy L. McKendree-Smith, PhD, and Graciela S. Alarcón, MD, MPH

Address
Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, School of Medicine, 475 Boshell Diabetes Building, 1808 7th Avenue South, Birmingham, AL 35294, USA.

E-mail: larry.bradley@ccc.uab.edu

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Individuals with fibromyalgia (FM) and/or chronic fatigue syndrome (CFS) report arthralgias and myalgias. However, only persons with FM alone exhibit abnormal pain responses to mild levels of stimulation, or allodynia. We identify the abnormalities in the neuroendocrine axes that are common to FM and CFS as well as the abnormalities in central neuropeptide levels and functional brain activity that differentiate these disorders. These two sets of factors, respectively, may account for the similiarities and differences in the pain experiences of persons with FM and CFS.

Fibromyalgia and CFS are disorders characterized by a wide array of somatic symptoms in the absence of biological diagnostic markers that might be used to distinguish them from one another and from other medical disorders [1••]. In addition, persons with FM and CFS frequently report that they experience similar symptoms, such as fatigue, nonrestorative sleep, and psychological distress [2,3]. However, arthralgias, myalgias, and other pain complaints show the greatest overlap between sufferers with FM and CFS. Indeed, studies of population-based samples as well as patient groups reveal that over 90% of persons with CFS report that they experience the primary symptom of FM, *ie*, persistent musculoskeletal pain [2–4].

This overlap in painful symptoms has led many health care professionals to believe that FM and CFS may be variations of the same disorder. However, only a few investigators have compared samples of individuals with FM and CFS on biological or psychosocial factors that might be related to their pain. We believe that it is necessary to carefully evaluate these research efforts in order to determine the extent to which the pathophysiology of FM and CFS overlap. The conclusions that are drawn from this research will have important consequences for both patient care and future research.

First we review the literature concerning the epidemiology of FM and CFS as well as the pain reports of persons with these disorders. Then we evaluate the investigations that have examined persons with FM and/or CFS on biological and psychosocial factors that may contribute to pain. These factors include 1) genetic predisposition to pain sensitivity; 2) the function of the hypothalamic-pituitary-adrenal (HPA) axis; 3) neuropeptides and brain structures involved in the processing or modulation of pain; and 4) the presence of psychiatric disorders (Table 1). We show that there is a great deal of overlap in the pain experiences as well as in the biological and psychosocial factors that characterize persons with FM and CFS. However, only individuals with FM display abnormal pain responses to mild stimuli as well as specific abnormalities in central levels of neuropeptides and the function of brain structures involved in pain transmission and modulation. These biological abnormalities may help account for the abnormal pain sensitivity found only in persons with FM.

Epidemiology of Fibromyalgia and Chronic Fatigue Syndrome

A small number of population-based studies in North America have established the prevalence rates for FM and CFS. The prevalence of FM ranges between 2% and 3% [5,6], whereas that for CFS varies between 0.2% and 0.4% [2,7–9]. Both disorders primarily affect women; it has been found consistently that women comprise about 90% of persons with FM and 70% of those with CFS.

Pain in Fibromyalgia and Chronic Fatigue Syndrome

Widespread and persistent pain is reported by all persons with FM and is quite common in individuals with CFS. A recent population-based study revealed that 94% of

Table 1. Biological and Psychological Factors Associated with Pain in Fibromyalgia and Chronic Fatigue Syndrome

Factor	Fibromyalgia	Chronic Fatigue Syndrome
Familial aggregation of painful symptoms	Consistent evidence of this phenomenon	Not studied
HPA-axis abnormalities	Lowered 24-h free urine cortisol	Lowered 24-h free urine cortisol
	Low CRH	Low CRH
	Low basal levels IGF-1 and growth hormone	No consistent abnormalities in IGF-1 or growth hormone
Neuropeptide levels	Low serum serotonin and low CSF 5-HIAA levels	High plasma 5-HIAA levels
	High CSF levels of substance P, dynorphin A, and CGRP	Normal CSF levels of substance P
Brain structure images	No cortical abnormalities	High number of cortical white matter lesions
Measures of functional brain activity	Hypoperfusion of the thalamus and caudate nucleus at rest	Brain stem hypoperfusion at rest
	Relatively low thalamic activation during painful stimulation	No studies of pain-induced brain activation
Psychiatric comorbidity	High frequency of depressive and anxiety disorders	High frequency of depressive and anxiety disorders

CGRP—calcitonin gene-related peptide; CRH—corticotropin-releasing hormone; CSF—cerebrospinal fluid; HPA— hypothalamic-pituitary-adrenal; IGF—insulin-like growth factor.

persons diagnosed with CFS report muscle aches or pain and 84% report joint pain [2]. The high frequency of pain in persons with CFS may be due, in part, to the inclusion of myalgias and arthralgias as two of the minor symptoms in the diagnostic criteria for this disorder established by the Centers for Disease Control and Prevention [10].

The epidemiologic studies cited previously have not attempted to determine the prevalence of persons who meet criteria for both FM and CFS. However, clinic-based investigations suggest that 35% to 70% of persons with CFS meet criteria for FM and 20% to 70% of individuals with FM also suffer from CFS [3,4,11–13]. Thus, there appears to be three subgroups of persons in the community with these disorders. These are persons with pain and fatigue who meet criteria only for CFS, those who meet criteria solely for FM, and those with both FM and CFS.

Buchwald [3] has shown that the tender point count reliably differentiates individuals in the latter two subgroups from those in the first subgroup. That is, only persons with FM or FM and CFS display abnormal pain responses to mild pressure stimulation at multiple anatomic sites, or allodynia. Their mean tender point counts are 12.4 and 13.1, respectively. They also show allodynia in response to numerous other sensory inputs, such as thermal stimulation [14]. However, persons with CFS alone produce a mean tender point count of 4.4; this is not substantially higher than the mean tender point counts in healthy controls, which range from 2.5 to 3.6 [14,15]. It currently is unknown whether these individuals might show abnormal pain responses to stimuli other than pressure. Next we examine the biological and psychological factors that might account for the presence or absence of allodynia in these subgroups.

Genetic Factors

Numerous investigators have proposed that there may be a genetic component to the development of painful symptoms in persons with FM and CFS [16]. However, nearly all of the empiric work performed in this area has been devoted to patients with FM. Family aggregation studies have shown that more than 50% of the first-degree relatives of patients with FM exhibit abnormal, tender point, pain responses and other findings consistent with FM [17–19]. These abnormalities are found primarily in the female relatives, which has led some investigators to suggest the influence of a sex-related, autosomal dominant genetic transmission of FM [19].

Indeed, two recent studies have produced modest evidence of a genetic linkage of FM to the histocompatibility locus antigen region [20] and to the promoter region of the serotonin transporter gene, 5-HTT [21]. In addition, animal research has revealed a striking dependence of sex differences in pain sensitivity and pain modulation on the genetic background of the animal subjects [22,23]. No relationships have yet been identified between sex-related genetic differences in pain transmission or modulation and the higher prevalence of FM in women compared with men. However, we believe it is quite likely that these associations will be identified among persons with FM in the future. We anticipate that these relationships also may be found among individuals with CFS, although they will probably be smaller in magnitude given the lower female to male ratio in this population.

Function of the Hypothalamic-Pituitary-Adrenal Axis

Efforts to understand the symptoms of FM and CFS have led researchers to study the neuroendocrine axes in patient

samples. Most of these investigators have attempted to study patients who meet criteria only for FM or CFS. No investigators have examined HPA axis function in patients with both FM and CFS. Nevertheless, it has been shown that both patients with FM and patients with CFS exhibit several markers of HPA axis dysregulation, such as relatively low levels of 24-hour urine-free cortisol and low hypothalamic levels of corticotropin-releasing hormone (CRH) [24–27]. Patients with FM and CFS also exhibit impairments in autonomic nervous system functions, such as abnormal response to orthostatic stress [28] and diminished sympathoadrenal responses to hypoglycemic challenge [29].

Abnormal CRH levels may be directly related to these impairments and to the painful symptoms reported by patients with FM and patients with CFS [30]. For example, CRH influences descending, antinociceptive pathways from the brain to the spinal dorsal horns through its effects on the sympathetic nervous system [16]. CRH also may diminish pain through its facilitating effects on glucocorticoid production and opioid-peptide secreting neurons in the hypothalamus that project to the brain stem and spinal cord [16,31]. Thus, abnormally low hypothalamic levels of CRH may disrupt the function of several biologic systems involved in pain modulation.

Abnormalities in the growth hormone (GH) axis also may contribute to the pain experiences of persons with FM. GH has its peak secretion during stage 4 of rapid eye movement (REM) sleep, and it is involved in the maintenance of muscle homeostasis. Bennett *et al.* [32] have proposed that the slow-wave sleep disorder documented in patients with FM [33] may lead to decreased GH secretion and, subsequently, to a vulnerability to muscle microtrauma and pain. It has been shown that patients with FM do show low basal levels of GH and insulin-like growth factor 1 (IGF-1) [34–37]. Furthermore, a placebo-controlled trial has shown that patients with FM display significant improvements in tender point scores and functional ability in response to GH injections [38].

The contribution of the GH axis to pain among persons with CFS is not clear. Bennett *et al.* [39] found elevated levels of IGF-1 in patients with CFS, whereas Allain *et al.* [40] reported lower levels of IGF-1 in an independent sample of these patients. Buchwald *et al.* [41] found no differences in IGF-1 and IGFBP-3 concentrations among healthy controls and patients who met criteria for CFS, FM, or both CFS and FM. All of these studies suffered from methodologic weaknesses such as small sample sizes or inadequate screening for comorbid disorders that might confound the results. Overall, then, there is stronger evidence for GH axis dysfunction in patients with FM than in patients with CFS.

Neuropeptides Related to Pain

Serotonin regulates the circadian fluctuations of the HPA axis [42] and probably plays a role in stimulating the release of CRH from the hypothalamus [43]. Moreover, it contributes to the activation of descending antinociceptive pathways from the brain to the spinal dorsal horns [16]. Several investigators have sought to determine whether low serotonin production might be associated with the painful symptoms of FM or CFS. Indeed, it has been found that patients with FM, compared with controls, exhibit abnormal metabolism of serotonin and its precursor tryptophan, lower serum levels of serotonin, and lower cerebrospinal fluid (CSF) levels of the serotonin metabolite, 5-HIAA [44–48]. In contrast, patients with CFS show increased plasma levels of 5-HIAA [49] and a prolactin response to buspirone indicative of enhanced serotonin neurotransmission [50].

Patients with FM and CFS also differ with respect to CSF levels of substance P. This neuropeptide facilitates nociceptive transmission in the periphery and in the central nervous system (CNS). Three studies have found that patients with FM, compared with controls, show elevated CSF substance P levels [51,52,53•]. In addition, one of these studies showed that community residents with FM who had not yet sought medical care for their pain (*ie*, nonpatients) also display abnormally high CSF levels of substance P. This finding indicates that abnormal CSF substance P is not produced by psychological distress because nonpatients do not differ from normal controls in psychiatric morbidity [15]. In contrast to the findings above in patients with FM, one recent study reported that the CSF levels of substance P in patients with CFS do not differ from the values produced by healthy controls [54].

Patients with FM also are characterized by elevated CSF levels of dynorphin A and calcitonin gene-related peptide or CGRP [55,56]. Elevated levels of these neuropeptides and substance P are consistent with changes in CNS function that have been observed after tissue injury. Under these circumstances, a series of events can occur that produce allodynia. One event is that new axon sprouts that are sensitive to stimulation often develop in the injured area of tissue. Spontaneous firings of these damaged nerves, as well as from the dorsal horn ganglion, increase the neuronal barrage into the CNS and contribute to the perception of pain. Similarly, spinal dorsal horn neurons also show increased excitability after injury, which is characterized by an enlargement of their peripheral receptive fields and enhanced responsiveness to mechanical, thermal, and chemical stimuli. This process of central sensitization, which also leads to increased neuronal input to the CNS, is mediated by activation of neurons with *N*-methyl-D-aspartate (NMDA) receptor sites by excitatory amino acids and is enhanced by neuropeptides such as dynorphin, substance P, and CGRP [57]. There currently is no direct evidence of functional changes in peripheral or spinal dorsal horn neurons in patients with FM. Laboratory studies, however, show that patients with FM display abnormal pain responses to low intensity stimuli that are consistent with the neuronal changes associated with central sensitization [58,59]. At present, no studies have

assessed whether patients with CFS might also show elevated CSF levels of dynorphin and CGRP or abnormal pain responses indicative of central sensitization.

It should be noted that stress may enhance the nociceptive effects of substance P release in persons with FM. It has been shown that CNS activation by stress stimulates mammotroph cells in the anterior pituitary to secrete prolactin and nerve growth factor (NGF) [60]. Consistent with these findings, patients with FM are characterized by elevated CSF levels of NGF [61]. Given that NGF regulates substance P expression in sensory nerves and may inhibit the antinociceptive effects of substance P metabolites [62], it is possible that stress contributes to pain or allodynia in persons with FM through its effects on NGF as well as on HPA axis function.

Brain Structures Involved in Pain Processing

Several investigators have attempted to identify abnormalities in brain structures that might contribute to the painful symptoms of FM and CFS. Their studies have focused on 1) MRI of brain structure and 2) functional neuroimaging of regional cerebral blood flow (rCBF) in brain structures that process or modulate pain.

MRI studies of brain structure

Nearly all of the investigations in this area have been performed on patients with CFS. The CFS studies are characterized by a high level of variation in the use of diagnostic criteria, controls for confounding variables such as history of head injury or neurologic signs at symptom onset, and statistical power [63] Nevertheless, three studies with adequate statistical power to detect differences between patients and controls found that patients with CFS display a significantly greater number of cortical white matter lesions [64–66]. A fourth study identified similar white matter abnormalities in patients with CFS, although the small sample sizes in this investigation probably accounted for the failure of this association to reach statistical significance [67]. Only one study with appropriate power failed to find a difference in white matter lesions between patients with CFS and controls [68]. We have performed MRI evaluations on 32 patients with FM, 13 nonpatients with FM, and 29 healthy controls prior to lumbar puncture [53•]. However, readings of these MRI images did not suggest an abnormally large number of white matter abnormalities in our subjects with FM.

Recently, several surgeons made claims in the media that a substantial number of patients with CFS and FM may experience pain, fatigue, and neurologic symptoms due to the presence of Chiari malformation or cervical spinal stenosis [69]. No controlled studies of a possible association between these structural abnormalities and CFS or FM have been published. However, we recently published an abstract of the preliminary findings of an investigation, which evaluated the presence of Chiari malformation in 30 rheumatology patients with FM, 12 nonpatients with FM, and 16 healthy controls [70,71].

Blinded MRI readings revealed that the Chiari malformation tended to be identified most frequently (20%) in the patients with FM ($P = 0.07$). Indeed, one of the six patients with FM with the Chiari malformation required neurosurgical intervention. Overall, however, the patients with Chiari malformation did not differ from patients and nonpatients without Chiari malformation with respect to self-reports of pain intensity or fatigue or in CSF levels of substance P. At present, then, the prevalence of the Chiari malformation in patients with FM and CFS is not known. Moreover, there presently are no peer-reviewed investigations in the literature regarding the extent to which 1) structural malformations of the cervical spine, such as the Chiari malformation may contribute to the painful symptoms experienced by these patients or 2) surgical interventions may relieve these patients' pain or fatigue.

Neuroimaging of functional brain activity

Single photon emission computed tomographic and positron emission tomographic imaging allow investigators to measure rCBF in brain structures either during rest or during exposure to stimuli that may evoke an increase in symptoms. All of the studies performed to date on patients with CFS have examined rCBF during rest conditions [72–78]. Six investigations have reported that patients with CFS, compared with controls, are characterized by significantly lower rCBF levels in numerous brain structures. There has been little agreement among these investigations regarding the specific brain structures that show hypoperfusion. However, two investigations found that patients with CFS, relative to controls, show significantly lower levels of rCBF in the brain stem; these findings were independent of depression [76,77]. Low brain stem rCBF levels may contribute to abnormal function of the locus ceruleus-norepinephrine/autonomic nervous system in patients with CFS. This abnormality, in turn, may be involved in the pain experiences of these patients, because the locus ceruleus is involved in controlling descending antinociceptive pathways from the brain to the spinal dorsal horns [16].

We have performed two studies of resting state rCBF in persons with FM. Our initial investigation revealed that patients, compared with controls, show significantly lower rCBF levels in the right and left thalamus and caudate nucleus [79]. It should be noted that similar abnormalities in thalamic rCBF have been observed in patients with chronic pain due to neuropathy [80] and metastatic cancer pain [81]. We have also found low levels of caudate rCBF in patients with painful restless leg syndrome [82]. We suggested, then, that low resting state levels of thalamic and caudate blood flow in patients with FM might be a compensatory neural response to prolonged periods of nociceptive input from the spinal dorsal horns [83•].

Our second study evaluated this hypothesis by examining resting state rCBF in clinic patients and nonpatients with FM as well as in healthy controls [84]. We found abnormally low rCBF in the thalami of patients with FM, regardless of whether

the onset of pain was insidious or associated with physical trauma. However, caudate abnormalities were found only in the patients and nonpatients who reported an insidious pain onset. As noted earlier, all groups with FM showed significantly higher CSF levels of substance P than controls. This is in accord with our hypothesis that prolonged nociceptive input, as indicated by elevated central levels of substance P, may produce the resting state abnormalities in thalamic rCBF found in persons with FM. However, factors associated with symptom onset may contribute to the presence of rCBF abnormalities in other brain structures, such as the caudate nucleus.

Finally, we recently reported our preliminary observations of the effects of painful pressure stimuli on brain responses in patients with FM with insidious pain onset. Given our resting state findings, we expected that these patients, compared with healthy controls, would show diminished thalamic and caudate response to painful stimulation. Indeed, our controls displayed significant rCBF increases in the contralateral thalamus and somatosensory cortex, whereas our patients exhibited bilateral and significant rCBF increases in the somatosensory cortex and significant ipsilateral rCBF increases in the anterior cingulate cortex [84]. Although all participants received stimulation that was calibrated to their respective pain threshold levels, the patients' ratings of stimulation intensity were twice that of the controls. It may be that the relatively low level of thalamic activation in the patients was associated with diminished modulation of nociceptive transmission from the spinal cord to cortical and other subcortical brain structures that process pain. This may have contributed to functional activation of the ipsilateral anterior cingulate cortex and widespread areas within the somatosensory cortex and, in turn, to the patients' high pain intensity ratings.

In summary, the neuroimaging studies described previously suggest that the pain experiences of patients with CFS may be related to low resting state levels of functional activity in the brain stem. This abnormality has not been documented in studies of patients with FM. However, patients with FM, compared with healthy persons, tend to show abnormal functional activity in several brain structures involved in the processing or modulation of pain. Abnormal thalamic activity occurs at rest and during exposure to noxious stimulation. It may be that the allodynia shown by patients with FM is related to diminished pain modulation function of the thalamus.

Psychiatric Comorbidity

Patients with FM and CFS suffer from significant psychiatric comorbidity, with depressive, anxiety, and somatization disorders being most prevalent [3]. Studies using structured psychiatric interviews indicate that 55% of patients with CFS meet criteria for a current Axis I diagnosis; up to one half have a current diagnosis of major depression, whereas two thirds have a lifetime history of this disorder [3]. Prevalence rates for current and lifetime psychiatric diagnoses are similar in patients with FM [15,85–88]. These findings have led some to suggest that CFS and FM are merely somatic presentations of depression [89,90].

In contrast, our studies of patients and nonpatients with FM indicate that high levels of psychiatric morbidity occur primarily in rheumatology clinic patients with FM. Nonpatients with FM do not differ from healthy persons in psychiatric morbidity [15], despite the fact that they show abnormalities in pain thresholds, CSF levels of substance P, and functional brain activity in the caudate nucleus at rest [53•]. Thus, psychiatric disorders alone cannot account for the abnormalities in pain sensitivity and biological factors noted previously. Nevertheless, we acknowledge that psychological distress is associated with the onset of painful symptoms in a substantial subgroup of persons with FM [83•]. It is possible, then, that psychiatric disorders or distress may contribute to the development of FM in this subgroup through their negative effects on HPA axis regulation.

Buchwald [3] has argued that psychiatric disorders cannot account for the symptoms of CFS because at least 25% of patients with this disorder have no lifetime psychiatric illness. Even in patients with CFS with major depression, most do not show the classic biological markers of this mood disorder, such as reduced REM latency or abnormal responses to the dexamethasone suppression test. Thus, it is unlikely that depression and other psychiatric disorders underlie the development of CFS.

Recent analyses of our cross-sectional data on patients and nonpatients with FM indicate that psychosocial factors, such as high levels of daily stress, trait anxiety, and maladaptive pain beliefs (*eg*, low self-efficacy), are the best independent predictors of status as a rheumatology clinic patient with FM [91]. Similarly, longitudinal follow-up of our nonpatients with FM reveals that work-related stress, psychiatric history of mood or substance abuse disorders, and use of prescription medication at baseline best predict the persons who seek medical care during the subsequent 30 months [92]. Thus, psychosocial factors appear to be important determinants of health care–seeking behavior in persons with FM. We believe that they may enhance pain sensitivity and suffering through their influence on brain limbic system activity and thus motivate persons with painful FM symptoms to consult physicians for treatment [93,94].

Models of the Pathogenesis of Fibromyalgia and Chronic Fatigue Syndrome

The literature reviewed previously indicates that patients with FM and CFS report similar painful symptoms. The pain responses of patients with CFS have not been studied as extensively as those of patients with FM. Nevertheless, pain threshold or tender point assessments suggest that although patients with FM display manifestations of allodynia, or the perception of pain in response to low

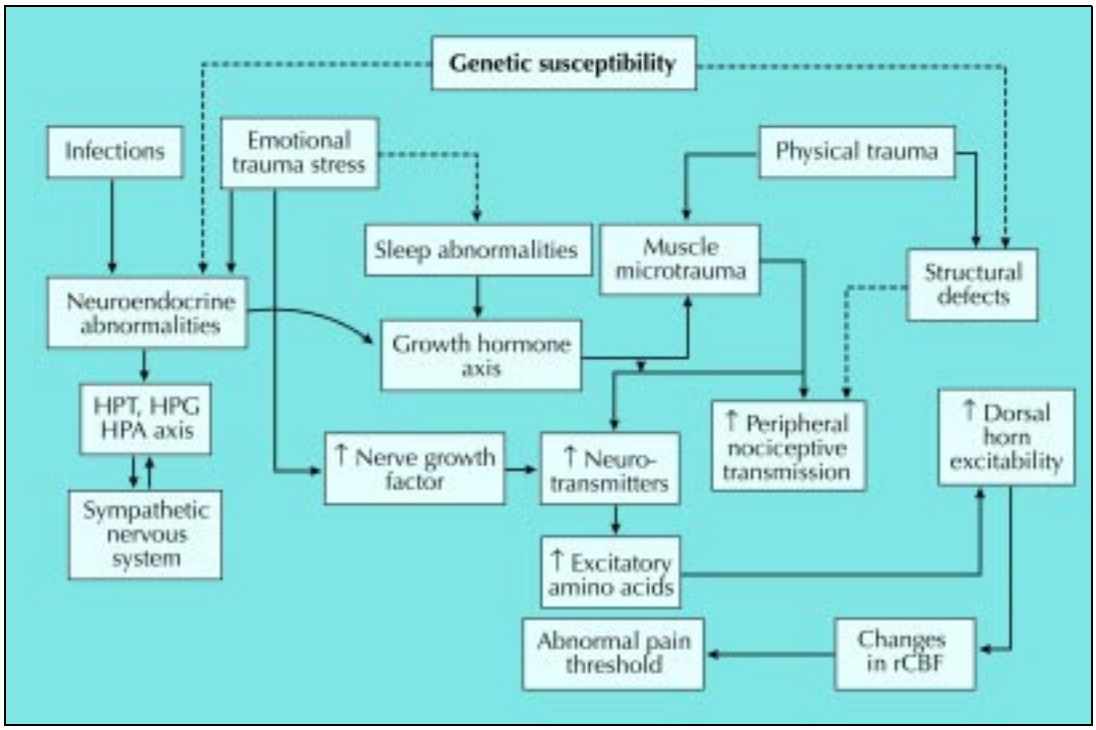

Figure 1. Model of the pathophysiology of abnormal pain sensitivity in fibromyalgia. *Solid lines* in this model represent established relationships and *dotted lines* represent relationships that are not yet well-established. HPA—hypothalamic-pituitary-adrenal; HPG—hypothalamic-pituitary-gonadal; HPT—hypothalamic-pituitary-thyroid; rCBF—regional cerebral blood flow.

intensity stimuli, only those patients with CFS who also meet the criteria for FM exhibit allodynia.

Investigators have devoted relatively little effort to the development of models of FM and CFS. Clauw and Chrousos [16], however, have suggested that patients with these disorders are genetically predisposed to the development of disorders characterized by pain and fatigue. A wide array of environmental triggers, such as emotional, physical, and immune stressors, may produce prolonged dysregulation in production of CRH and the locus ceruleus-norepinephrine/autonomic nervous systems. In any given individual, this dysregulation may lead to one or more of the following abnormalities: blunting of one or more of the HPA axes, altered nociceptive transmission or modulation, or instability of the autonomic nervous system. The symptoms produced by these abnormalities may be modulated by the presence of psychiatric illness or other psychosocial factors. Thus, the large number of combinations of abnormalities that may occur and the influence of psychosocial factors account for the heterogeneity of symptoms observed in persons with FM and CFS.

We independently developed a model of abnormal pain perception in FM that is quite similar to that above [83•]. This model suggests that both exogenous (*eg*, physical trauma) and endogenous (*eg*, neuroendocrine axes) abnormalities in genetically predisposed individuals lead to a final common pathway, *ie*, specific alterations in nociceptive transmission and neuropeptide production that underlie central sensitization (Fig. 1). The prolonged nociceptive input from the spinal cord to the brain that is produced by these alterations leads to functional abnormalities in the brain structures, such as the thalamus, that process or modulate pain transmission. In this model, psychiatric illness and other psychosocial factors may be involved in the development of abnormal pain perception in some persons as well as influence individuals' pain experiences.

Why do some predisposed individuals meet criteria for both of these disorders whereas others meet criteria only for FM or CFS? We currently cannot answer this question with confidence. However, Melzack's [94] recent revision of the gate control theory provides a model for investigation of this issue [95]. The revised theory suggests that brain pathways linking the thalamus, cortex, and limbic system form a neuromatrix that generates perceptions of pain and pain behavior. Figure 2 shows that multiple endogenous and exogenous factors may influence the functioning of the neuromatrix. Disorders characterized by chronic pain are produced by alterations in the neuromatrix that cannot be restored to normal functioning. It may be, then, that persons with FM and CFS are characterized by dysregulation of CRH production and the locus ceruleus-norepinephrine/autonomic nervous systems. This may account for the experience of myalgias and arthralgias in individuals with both disorders. However, the biological and psychosocial factors shown in Figures 1 and 2 combine to produce central sensitization and allodynia in only some of these individuals. Persons with debilitating fatigue without allodynia may receive the diagnosis of CFS, whereas those with allodynia and relatively low fatigue levels may receive the diagnosis of FM. Individuals with high levels of fatigue and allodynia may receive both diagnoses.

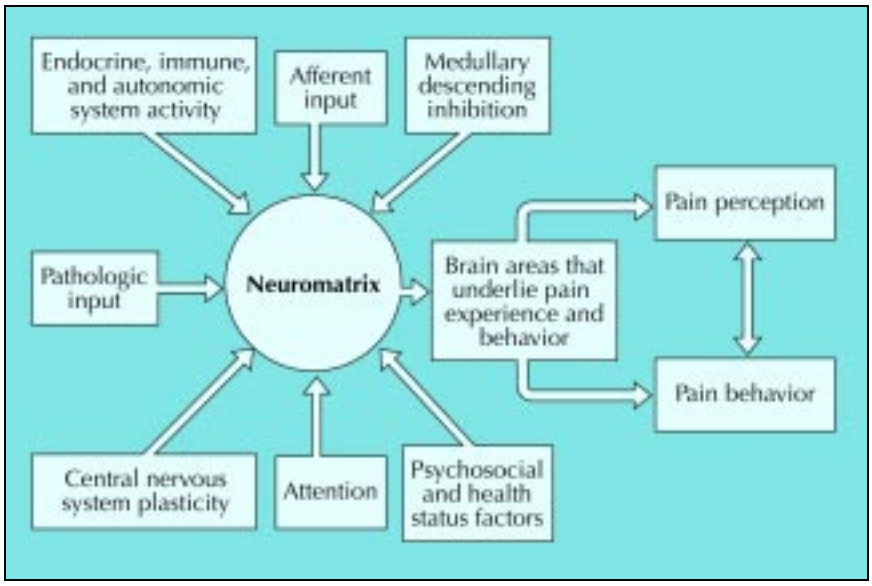

Figure 2. Model of the neuromatrix. The neuromatrix is a widespread network of brain neurons that generates patterns of activity responsible for perceptions of pain as well as reflexive and complex pain behaviors. We propose that disorders characterized by persistent pain, such as fibromyalgia and chronic fatigue syndrome, are produced by pathologic alterations in the nervous system and neuromatrix that cannot be restored to normal functioning. (*Adapted from* Melzack [94].)

Implications for Research and Treatment

The literature reviewed previously has led to the development of a small number of models of the development of pain and other symptoms in FM and CFS. However, relatively little work has been performed to test hypotheses based on these models. The methodologic problems associated with the study of these disorders may account in part for the dearth of theory-driven research. For example, we currently are testing several hypotheses regarding the factors that influence pain reports and the brain responses of patients with FM, CFS, and major depression, as well as those of healthy controls to noxious stimulation. This work requires us to 1) recruit only patients who meet criteria for FM or CFS but not both disorders; 2) ensure that the patients with major depression do not experience chronic pain or meet criteria for FM or CFS; 3) ensure that subjects are comparable in demographic factors such as age, sex, and education level; and 4) washout psychoactive and pain-modulating medications.

These methodologic requirements can be quite frustrating to investigators who are rewarded for rapid production of publishable findings. They are necessary, however, if we are to better understand the development of persistent pain or allodynia in persons with FM and CFS. We encourage investigators to engage in similar work; we also implore federal and private agencies to support these efforts and to provide sufficient funds to perform the careful screening needed to ensure valid findings.

The models also have important implications for treatment-related research. For example, the permanent alterations in the activity of the neuromatrix, which are posited to underlie allodynia in patients with FM, may help account for the failure of investigators to show that cognitive-behavioral therapies produce improvements in pain that are superior to those effected by an attention-placebo [96]. These alterations may also help explain the relatively modest and short-lived improvements in pain associated with the use of exercise, tricyclic antidepressants, and selective serotonin reuptake inhibitors in patients with FM and CFS [97]. That is, altering behavior or central levels of neuropeptides may not be sufficient to substantially alter the abnormal activity of the neuromatrix in these patients. Thus, it appears necessary to develop and test new, centrally acting pharmacologic agents that will alter biological processes that are involved in the development of pain in FM and CFS. Some work, involving the NMDA receptor and substance P antagonists, is feasible at the present time. Eventually, it will be possible to evaluate the effects of new drug therapies on patients with FM or CFS and to assess the extent to which cognitive-behavioral interventions may potentiate the beneficial effects of these therapies. The long-term goal should be to determine the combinations of pharmacologic, exercise, and cognitive-behavioral therapies that are most effective for specific subgroups of patients with these disorders.

Conclusions

To conclude, the preceding review shows that substantial progress has been made in understanding the pathophysiology of pain in patients with FM and CFS. We now have testable models that may be used to further this understanding and to develop treatments that may produce clinically meaningful and sustained improvements in these patients' pain experiences. We look forward to participating in this work and to helping our patients benefit from our efforts and those of other investigators.

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Recently published papers of particular interest are highlighted as:

- • Of special interest
- •• Of outstanding interest

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